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MIB-1 Labeling Index (Ki67) of Gastric Type Intraductal Papillary-Mucinous Neoplasms of the Pancreas

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ABSTRACT

Purpose: This study examined the relationship between the MIB-1 labeling index (Ki67) and the four morphological and immunohistological subtypes of intraductal papillary-mucinous neoplasms of the pancreas (IPMN).

Methods: Between 2000 and 2007, we retrospectively evaluated 46 patients who had undergone surgery, were histopathologically diagnosed as IPMN, and in whom immunohistochemical staining was possible.

Results: Histological grades of the 46 IPMNs were adenoma (n = 27), carcinoma in situ (n = 9), and invasive carcinoma derived from IPMN (n = 10). The morphological and immunohistological subtypes were gastric (n = 20), intestinal (n =15), panacreatobiliary (n = 9), and oncocytic (n = 2). The overall MIB-1 labeling index was 8.63% ± 9.16%. The MIB-1 labeling index of the gastric type was 3.99 ± 6.78%, which was significantly less than that of the intestinal (11.83 ± 8.95%) and pancreatobiliary (11.30 ± 10.35%) types. The MIB-1 labeling index of patients with adenoma and the gastric type was less than that for patients with adenoma and the intestinal type (p = 0.04). There were no disease-specific fatalities in patients with an MIB-1 labeling index of <10%, whereas in those with an index of ≥ 10%, the 5-year survival rate was 61.1% and the prognosis was poor.

Conclusions: gastric type IPMN have a low MIB-1 labeling index, which demonstrates that malignancy of this subtype is lower than that of other subtypes.

Key words : MIB-1 labeling index, Ki67, histological grade, gastric type, intraductal papillary-mucinous neoplasms

Introduction

Intraductal papillary-mucinous neoplasms (lPMNs) are tumors that are classified as true neoplastic cysts of the pancreas. IPMNs are characterized by large quantities of mucous production, opening of Vater's papilla, pancreatic duct dilation, papillomatous proliferation of the pancreatic duct, and poor infiltration. Although prognosis is excellent in noninvasive cases, the postoperative 5-year survival rate of invasive cases is 40%−50%. The male to female ratio is 2:1. IPMNs are common among elderly individuals (mean age for both genders, approximately 65 years). The preferred site of IPMNs is the pancreatic head, which accounts for up to 70% of cases[1].

The concept of an IPMN was first reported by Ohhashi et al[2], who described it as a ''mucin-producing pancreatic tumor.'' Since 1990, this

disease concept has been confirmed worldwide by the Japanese Classification of Pancreatic Carcinoma[3], the Armed Forces Institute of Pathology[4], the International Histological Typing of Tumors of the Exocrine Pancreas by the World Health Organization[5], and by Kimura et al[6-8]. Moreover the International Consensus Guidelines for Management of IPMNs were published in 2006[9]. In recent years, the concept of a new classification of IPMNs, based on immunohistological subtypes, which was revised according to the WHO classification in 2010, has been adopted[11], and the international consensus guidelines of 2012 for the management of IPMN and MCN of the pancreas have been published[10].

Our group, Takasu et al[12] previously reported a retrospective comparative study of the clinicopathological features, degree of malignancy, morphological and immunohistological findings and prognosis of IPMNs. That study divided IPMNs into the following four subtypes: gastric, intestinal, pancreatobiliary, and oncocytic. Furthermore, IPMNs were histopathologically classified as adenoma/borderline (IPMN with low- or intermediate-grade dysplasia), carcinoma in situ (IPMN with high-grade dysplasia), or invasive carcinoma derived from IPMN (IPMN with an associated invasive carcinoma), in which cancer development was described according to staging. Moreover, Takeshita et al[13] from our group reported that an MIB-1 labeling index (Ki67) could be used as an indicator of the degree of malignancy. However, there has not yet been any study in which the association between the MIB-1 labeling index (Ki67) and the four morphological and immunohistological subtypes was investigated. The present study therefore aimed to examine the relationship between the MIB-1 labeling index (Ki67) and the four morphological and immunohistological IPMN subtypes described above.

Materials and Methods

Patients

Between 2000 and 2007, we retrospectively evaluated 46 patients who had undergone surgery at the Department of Gastroenterological and General Surgery, Yamagata University, Faculty of Medicine, Japan, were histopathologically diagnosed as IPMN, and in whom immunohistochemical staining was possible. Clinical and follow-up information was obtained from patient charts.

Subclassification of IPMNs

The 46 IPMN patients were graded as adenoma/borderline (adenoma, in this paper), carcinoma in situ, or invasive carcinoma derived from IPMN according to their histological grade. This grading corresponded to the WHO IPMN subtype classification[11] of IPMN with low-/intermediate-grade dysplasia, IPMN with high-grade dysplasia, and IPMN with an associated invasive carcinoma, respectively. Adenoma (IPMN with low- or intermediate-grade dysplasia) showed papillary growth, consisted of a higher proportion of columnar cells than the other subtypes, and maintained a proper nuclear arrangement as assessed by hematoxylin and eosin (H-E) staining. Carcinoma in situ (IPMN with high-grade dysplasia) showed a lack of proper nuclear arrangement, enlargement of the nucleus, a definite nuclear pole, and a high level of mitosis. We defined invasive carcinoma derived from IPMN (IPMN with an associated invasive carcinoma) as cancer cells that infiltrated the basal membrane and invaded interstitial connective tissue.

The 46 cases of IPMN were subclassified into 4 types (Gastric, Intestinal, Pancreatobiliary, and Oncocytic) as described by Furukawa et al[14] on the basis of their morphological features and their immunohistochemical reactivity (MUC1, MUC2, and MUC5AC staining). The samples were first classified on the basis of their H-E stained findings, after which immunohistochemical analysis was performed to confirm the results. When the assessment made on the basis of H-E staining was inconsistent with the immunohistochemicaldata, the H-E stained slides were rechecked. If the H-E data remained inconsistent with the immunohistochemical analysis, the H-E based assessment was used rather than the immunohistochemical based assessment[12].

Immunohistochemical staining

Immunohistological staining was performed using the streptavidin-biotin method. Resected specimens

were fixed with formalin and embedded in paraffin. Thin serial sections were made with a microtome. After deparaffinization, sliced specimens were washed with phosphate-buffered saline. The specimens were then heated three times in a microwave at 900 W for a total of 30 minutes at 100°C. Endogenous peroxidase was blocked with 0.3% H_2O_2. Non-specific staining was blocked by incubating the sections in a solution containing 3% skim milk. The sections were subsequently incubated with primary antibody overnight at 4°C. Next, the sections were incubated with a second biotinylated mouse monoclonal antibody and peroxidase-labeled streptavidin (LSAB kit; Dako, Glostrup, Denmark) for 1 hour. Peroxidase activity was then detected using 3,3'-diaminobenzidine. Finally, counterstaining was performed with hematoxylin. The primary antibodies used were specific for MUC1 (clone Ma695; dilution 1:100) (NovoCastra Laboratories, Newcastle upon Tyne, UK), MUC2 (clone Cep58; dilution 1:200) (NovoCastra Laboratories), MUC5AC (clone CLH2; dilution 1:100) (NovoCastra Laboratories), or the Ki67 antigen (clone MIB-1; dilution 1:120) (Dako, Glostrup, Denmark).

Evaluation of MUC1, MUC2, and MUC5AC staining

Two to four slides were immunohistochemically stained per case. The entire neoplasm on each slide was microscopically examined under low power (×10) and the approximate percentage of positively stained neoplastic cells was calculated. The neoplasms were graded as follows: (-) less than 5% of neoplastic cells positive, (+) 5% to 50% of neoplastic cells positive, and (++) more than 50% of neoplastic cells positive. For invasive carcinoma derived from IPMN, only the noninvasive sites were evaluated: sites of apparent invasion were not assessed.

Evaluation of MIB-1 staining

Two to three slides were immunohistochemically stained per case. More than 5 fields were selected at random and microscopically analyzed. In one particular case, five areas were chosen and analyzed at a higher magnification (×200). More than 2000 tumor cells were countedper case. The MIB-1 labeling index was calculated as the percentage (%) of the total tumor cells that stained positive. In invasive carcinoma derived from IPMN, only the noninvasive sites were evaluated: sites of apparent invasion were not assessed.

All of the pathological and immunohistochemical investigations of IPMNs were performed, and the results were confirmed, by two physicians.

Statistical analysis

Results are expressed as means ± SD (range). Continuous variables were analyzed using Student's *t*-test. Survival was calculated from the date of resection to the date of disease-specific fatality or to the date of censoring at the last follow-up. Cumulative overall survival rates were calculated using the Kaplan-Meier method. Statistical significance was defined as $P < 0.05$. All analyses were carried out using the StatView version 5.0 Software of the SAS Institute, Inc.

Results

Patient clinicopathological characteristics (n = 46) are shown in Table 1. The mean age of the patients (32 males and 14 females) was 67 ± 10 years (range, 47−87). Pancreaticoduodenectomy[15] was performed in 26 patients, distal pancreatectomy with splenectomy in 9, spleen-preserving distal pancreatectomy[16] in 10, and total pancreatectomy in one patient. Histological grade was: adenoma (n = 27), carcinoma in situ (n = 9), and invasive carcinoma derived from IPMN (n = 10). Subtypes, based on morphological features and immunohistochemical reactivity, were as follows: gastric (n = 20), intestinal (n =15), panacreatobiliary (n = 9), and oncocytic (n = 2). The overall MIB-1 labeling index for all patients was 8.6% ± 9.2% (range, 0.34%− 29%). The MIB-1 labeling index (Ki67) of patients with the gastric type was 4.0% ± 6.8%, which was significantly less than that for patients with intestinal or pancreatobiliary types (Figure 1). In patients with the gastric type there were significantly more adenomas observed (n = 17, 86%) than carcinomas in situ (n = 3) or invasive carcinomas derived from IPMN (n = 0) (Table 2). Similar numbers of each histological gradeof tumor were found in the intestinal type. Adenomas and invasive

Table 1. Clinicopathological characteristics of 46 IPMN patients

No.	46
Age (mean ± SD)	67 ± 10
Sex	
Men	32
Women	14
Tumor location	
Head	25
Body and/or tail	20
Whole	1
Macroscopic subtype	
Branch duct type	35
Main duct type	4
Mixed type	7
Operative procedure	
PD	26
DPS	9
SPDP	10
TP	1
Histological grade	
Adenoma	27
Carcinoma in situ	9
Invasive carcinoma derived from IPMN	10
Observation period (mean ± SD)	69 ± 37
Disease-specific fatality (n)	7
Five-year survival rate (%)	84.3%

PD, pancreaticoduodenectomy; DPS, distal pancreatectomy with splenectomy, SPDP, spleen-preserving distal pancreatectomy; TP, total pancreatectomy; Adenoma, IPMN with low- or intermediate-grade dysplasia, adenoma, or borderline; Carcinoma in situ, IPMN with high-grade dysplasia or non-invasive carcinoma; Invasive carcinoma derived from IPMN, IPMN with an associated invasive carcinoma.

carcinomas derived from IPMN were the most common histological grades found in the pancreatobiliary type (both, n = 4). The MIB-1 labeling index (Ki67) of patients with adenoma and the gastric type of IPMN was less than that for patients with adenoma and the intestinal type of IPMN (p = 0.04). There was no significant difference between the MIB-1 labeling index of patients with carcinoma in situ and the gastric type of IPMN and that for patients with carcinoma in situ and the intestinal type of IPMN. The survival curve for all 46 patients with IPMN is shown in Figure 2. The mean observation period was 68.6 ± 36.9 months (range, 6–153 months). There were seven disease-specific fatalities, all of which were invasive carcinomas derived from IPMN, including 1, 4, and 2 patients with intestinal, pancreatobiliary, and oncocytic subtypes, respectively. The 5-year overall survival rate was 84.3%.

The relationship between survival and MIB-1 labeling indices of <10% and ≥ 10% is shown in Figure 3. There were no disease-specific fatalities in patients with an MIB-1 labeling index of <10%, whereas in those with an index of ≥ 10%, the 5-year survival rate was 61.1% and the prognosis was apparently poor.

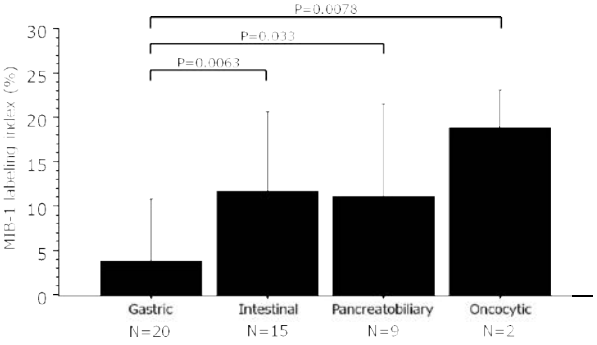

Figure 1. MIB-1 labeling indices of each immunohistological subtype of IPMN

Data are shown as means (thick bars) + standard deviations (thin bars).

The MIB-1 labeling index (Ki67) of patients with the gastric type was significantly less than that for patients with intestinal or pancreatobiliary types.

Table 2. Histological grading and MIB-1 labeling index (Ki67) of IPMNs according to immunohistological subtypes

	Gastric	Intestinal	Pancreatobiliary	Oncocytic
Adenoma				
N	17	6	4	0
MIB-1 labeling index(%)	1.47 ± 1.12 (0.34-4.01)	3.72 ± 3.65 (0.69-9.95)	1.17 ± 0.54 (0.75-1.92)	-
		p=0.04		
Carcinoma in situ				
N	3	5	1	0
MIB-1 labeling index(%)	18.26 ± 9.49 (11.02-29)	15.42 ± 7.68 (4.21-23.21)	11.06*	-
		NS		
Invasive carcinoma derived from IPMN				
N	0	4	4	2
MIB-1 labeling index(%)	-	19.50 ± 6.40 (13-25)	21.50 ± 3.11 (18-25)	16,22*
Total				
N	20	15	9	2
MIB-1 labeling index(%)	3.99 ± 6.78 (0.34-29)	11.83 ± 8.95 (0.69-25)	11.30 ± 10.35 (0.75-25)	16,22*

Adenoma, IPMN with low- or intermediate-grade dysplasia, adenoma, or borderline; Carcinoma in situ, IPMN with high-grade dysplasia or non-invasive carcinoma; Invasive carcinoma derived from IPMN, IPMN with an associated invasive carcinoma; NS, no significant. MIB-1 labeling indexes are expressed as mean ± standard deviation.
* showing actual values.

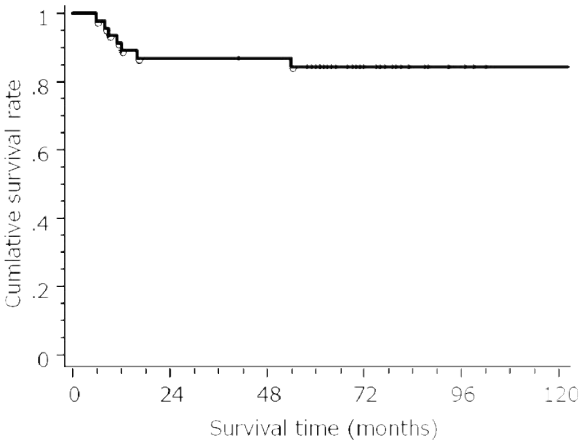

Figure 2. Survival curves of all 46 patients with IPMN
The mean observation period was 68.6 ± 36.9 months, and the 5-year survival rate was 84.3%.

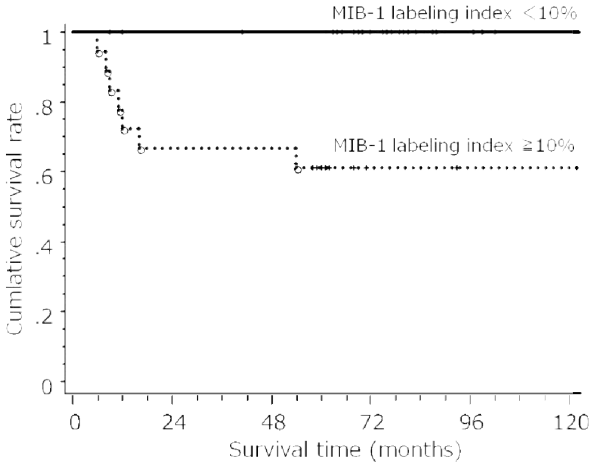

Figure 3. Correlation of survival curves with MIB-1 labeling indices of < 10% and ≥ 10%
There were no disease-specific fatalities in patients with an MIB-1 labeling index of <10%, whereas in those with an index of ≥ 10%, the 5-year survival rate was 61.1% and the prognosis was poor.

Discussion

Various gastrointestinal cancers are classified according to cell and tissue morphology and a correlation with clinicopathological characteristics and prognosis is acknowledged. Lauren[17] classified gastric carcinoma into diffuse and intestinal types and demonstrated that these types correlated with clinical characteristics. Kimura et al[18] were the first to use the terms intestinal type and pancreatobiliary type in carcinoma of the papilla of Vater, and they reported that cases of the pancreatobiliary type had a worse prognosis than those of the intestinal type.

The following two classification systems were created for IPMNs: Adsay et al[19] divided the condition into intestinal, pancreatobiliary, and null types, whereas Yonezawa et al[20] created two categories: villous dark cell and papillary clear cell types. In a further report by Adsay et al[21], these authors described the concept of intraductal oncocytic papillary neoplasms, in which the papilla, comprising eosinophilic cells, exhibits a complex branching form. In 2005, Furukawa et al[14] reported a consensus study regarding a new IPMN classification that integrated these two schools of thought, in which IPMN was classified into the following four subtypes: gastric, intestinal, pancreatobiliary, and oncocytic. This concept was adopted by WHO as their new classification system in 2010[11]. We classified the 46 patients in our study into four subtypes according to the classification system of Furukawa et al[14]. According to this system, the histopathological subtype of IPMN should first be based on morphological characteristics and then confirmed by immunohistological staining. Our study was based on this concept. When findings from H-E staining differed from those of immunohistological staining, we based the classification on both H-E staining and the pathological findings collected from at least two physicians. However, only a few such cases were found in this study. In our group, the prognosis of patients with the gastric or intestinal types was more favorable than that for patients with the pancreatobiliary type[12]. Moreover, the prognosis of patients with invasive carcinomas derived from IPMN tended to be better for the intestinal type than for the pancreatobiliary type, which may suggest that the former is a slow-growing neoplasm.

IPMN grading for atypia was histopathologically classified into adenoma (IPMN with low- or intermediate-grade dysplasia), carcinoma in situ (IPMN with high-grade dysplasia), or invasive carcinoma derived from IPMN (IPMN with an associated invasive carcinoma), in which cancer development is described according to staging. Takeshita et al[13] demonstrated that the MIB-1 labeling index, Ki67, was higher for patients with carcinoma in situ than for patients with adenoma; thus, the MIB-1 labeling index was considered as an appropriate indicator of the degree of malignancy. These authors also suggested that when IPMN is diagnosed as carcinoma in situ, it should be surgically removed.

On the basis of these two reports, we examined the relationship between the MIB-1 labeling index, Ki67, which is an indicator of malignancy, and the four different morphological and immunohistological subtypes of IPMN. We found that the MIB-1 labeling index of patients with the gastric type was significantly lower than that of patients with the other subtypes (Figure 1). Moreover, of the 46 patients, those with an MIB-1 labeling index of less than 10% showed no decrease in survival time after surgery (Figure 3). In summary, our findings regarding the MIB-1 labeling index demonstrate that patients with the gastric type, who have a low MIB-1 index, exhibited a lower degree of malignancy than those with other subtypes, who have a higher MIB-1 index, and that their prognosis was good.

Similarly, Furukawa et al[22] also demonstrated that overall prognosis was better for patients with the gastric type of IPMN than for patients with other IPMN subtypes. It has been postulated that gastric type IPMN often displays low- or intermediate-grade dysplasia and that malignant transition occurs less-frequently in patients with gastric type IPMN[10, 11]. In the present study, although adenoma was frequently found in patients with gastric type IPMN, invasive carcinoma derived from IPMN was not found in these patients. On the other hand, some previous studies have shown that patients with invasive carcinoma derived from gastric type IPMN, which often takes the histological finding of tubular adenocarcinoma, have a worse prognosis than patients with invasive carcinoma derived from intestinal type IPMN[22, 23]. In 2002, Adsay et al[26] suggested that MUC2-positive IPMN, i.e. the intestinal type, whose carcinogenesis follows a pathway similar to the adenoma-carcinoma sequence in colorectal cancer, is "indolent" disease, whereas MUC1 positive IPMN, i.e. the pancreatobiliary type, is "aggressive" disease similar to pancreatic adenocarcinoma. In addition, there is increasing evidence that gastric type IPMN shows a significantly higher incidence of KRAS mutations[24], and no incidence of GNAS mutation compared with the

intestinal type[25]. It has been suggested that the carcinogenesis of not only the pancreatobiliary type but also the gastric type of IPMN may be the same as that of pancreatic adenocarcinoma[24), 25)]. In the light of these studies, it is interesting to note that the MIB-1 labeling index of patients with the gastric type differed from that of the intestinal type in this study.

In the present study, no invasive carcinoma derived from IPMN was detected in patients with the gastric type, and the MIB-1 labeling index of this type was significantly less than that of the other subtypes. These results may be due to a difference in histological grade of the neoplasm. However, the MIB-1 labeling index of patients with the gastric type was only less than that of patients with the intestinal type for neoplasms that were graded as adenomas. We concluded that malignancy of the gastric type of IPMN not higher and may be lower than that of other subtypes. Although patients with the gastric type of invasive carcinomas derived from IPMN may have poor prognoses[22), 23)], such cases were not found in this study of 46 cases. We therefore suggest that such cases may be rare and, consequently, more of such cases should be accumulated for further study.

In conclusion, gastric type intraductal papillary mucinous neoplasms have a low MIB-1 labeling index, which demonstrates that malignancy of this subtype is lower than that of other subtypes.

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